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Neonatal Pain-related Stress, Neonatal Structural Brain Subnetworks, Cortisol and Behavior at 4 years in Children Born Very Preterm

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Internalizing behaviors (anxiety, depressive symptoms) and executive function difficulties are prevalent in children born very preterm (≤ 32 weeks gestation). Procedural pain/stress during hospitalization is associated with regionally-specific neonatal brain microstructure alterations, hypothalamic-pituitary-adrenal (HPA) axis functioning (cortisol), and behavior problems in childhood. Here we investigate the interplay between early pain/stress, structural brain organisation, and cortisol dysregulation in relation to child internalizing behaviors and executive function. Current study includes N = 50 infants born very preterm with neonatal chart review (e.g. pain/stress [number of invasive procedures], infection), whole-brain tractography in early life and term equivalent age (MRI/DTI) to measure change in streamline count between 90 cortical and subcortical regions normalized by total number of streamlines, and parent report of internalizing behaviors and executive functioning and salivary cortisol samples at 4-years. Whole-brain network integration (global efficiency) and segregation (transitivity) decreased with greater neonatal pain/stress. Partial-Least Squares Correlation analysis showed clinical factors including neonatal pain/stress were related to change in 128 region-pair connections (normalized streamline count; 69% intrahemispheric, 82% cortico-cortical) across the neonatal period, accounting for 45% covariance between latent factors. Relative to weeks between scans, smaller increases in connectivity were primarily related to frontal-limbic (25%) regions, with less of a decrease in frontal-limbic (14%) and frontal-temporal (15%) regions. Subsequent analyses to 4-year behavior and cortisol in progress. Our study advances understanding of the effects of early life stress on brain circuitry during a critical developmental window of early life. Findings will elucidate how such alterations impact behavior, considering physiological stress regulation.